Acute Lung Injury and Acute Respiratory Distress Syndrome

University of Minnesota*
Dewey H. Carpenter, Jr., DVM

Auburn University
Douglass K. Macintire, DVM, DACVIM, DACVECC

Mississippi State University
John W. Tyler, DVM, DACVIM

ABSTRACT: Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are severe respiratory diseases that have not been well characterized in veterinary medicine. Despite extensive research into this area in human medicine over the past 30 years, little is known about the exact pathogenesis of this complex syndrome. With the increase in veterinary critical care facilities and the greater number of owners who are willing to enter into extensive treatment of critically ill animals, there will also be an increase in the number of ALI/ARDS cases that are identified and treated. Therefore, it is essential for veterinarians not only to recognize the clinical signs of ALI/ARDS but also to know the risk factors that may predispose patients to developing these respiratory diseases. Knowledge of the complex pathophysiology as well as the pathogenesis is also required to anticipate changes in the animal’s condition. To date, treatment remains primarily symptomatic and is aimed at improving oxygenation. This article is intended to provide clinicians with a basic understanding of the risk factors, pathophysiology, pathogenesis, clinical signs, and treatments that may help improve the survival of veterinary patients with ALI/ARDS.

Acute respiratory distress syndrome (ARDS), originally called adult respiratory distress syndrome, was first recognized as a clinical disorder in human intensive care patients by Ashbaugh and colleagues in 1967. It was defined as a clinical syndrome characterized by severe hypoxemia refractory to oxygen treatment with patchy bilateral alveolar infiltrates on chest radiographs and low pulmonary compliance. Estimates of prevalence in humans range from 1.5 to 75 per 100,000 patients; but most experts believe that the actual prevalence is about 5 to 7 per 100,000. Most of the disparity in mortality and prevalence studies has come from the varying definitions of ARDS over the past 30 years. In 1994, an American-European Consensus Committee on ARDS differentiated acute lung injury (ALI) from ARDS by establishing clinical diagnostic criteria for each condition. Differentiation is based on the ratio of partial pressure of arterial oxygen to fractional inspired oxygen (PaO₂:FiO₂). A value of

*When this article was written, Dr. Carpenter was at Auburn University.
less than 300 indicates ALI and less than 200 indicates ARDS. Consequently, all ALI cases do not result in ARDS, but all cases of ARDS will result from ALI.

Despite being one of the most researched areas of human medicine in the past 20 years, little is known about the exact initiating causes and the best methods of treatment for ALI/ARDS. A single inciting event responsible for producing the clinical signs of ARDS has not been found. It appears more likely that a multitude of events occurs, and any of these can lead to the development of ALI/ARDS. This supposition would coincide with the multiple unrelated risk factors that can lead to the development of this clinical syndrome.

Dogs are used extensively in experimental models for studying the development of ARDS associated with pancreatitis, paraquat poisoning, ethchlorvynol toxicosis, trauma, oleic acid injury, and endotoxemia. However, these studies often look at only a single aspect of the entire syndrome, thus making the information less applicable to the clinical veterinary setting. In addition, only isolated case reports and review articles have been published in the veterinary literature.

With the advent of more advanced emergency and critical care facilities as well as an increased availability of advanced diagnostic capabilities in veterinary medicine, it is likely that more cases of ALI/ARDS will be identified and treated. However, little is known about the actual prevalence and mortality resulting from ALI/ARDS in dogs. It must be assumed that the mortality rate is much higher than is seen in human populations because of the limited long-term ventilatory capabilities in veterinary medicine. More information is needed to establish the clinical differences between human and canine patients with ALI/ARDS.

**RISK FACTORS**

There are numerous recognized causes of ALI in humans. These causes are generally placed into two categories: direct and indirect lung injury. Common causes of direct lung injury in dogs include aspiration of gastric contents, blunt force trauma with pulmonary contusions, near drowning, inhalation of noxious gases (e.g., smoke inhalation injury), oxygen toxicity, and pneumonia. These injuries are often progressive, and their severity should not be underestimated based on initial clinical parameters.

Indirect lung injury in humans commonly results from systemic inflammatory response syndrome (SIRS) and may or may not be related to sepsis. In dogs, indirect or secondary lung injury has been associated with sepsis, SIRS, shock, trauma, pancreatitis, parvoviral enteritis, organ torsion, and paraquat toxicosis. Parent and colleagues identified microbial pneumonia, sepsis, and aspiration pneumonia as the most common risk factors observed in dogs. Other predisposing factors observed in order of prevalence were nonresponsive shock, oxygen toxicity, organ torsion, laryngeal obstruction secondary to strangulation with a choke chain, pulmonary trauma, and disseminated intravascular coagulation (DIC). Of the dogs in this study, 58% had more than one risk factor present and 33% had three or more risk factors. This is comparable to the increased risk seen in human patients that have two or more predisposing factors.

Acute respiratory distress syndrome is now considered a risk factor for the development of SIRS and multisystem organ failure syndrome (MOFS). In fact, several experts believe that ARDS is not a single organ failure syndrome but the first organ to fail in MOFS and is closely followed by liver dysfunction. About 20% of human patients with ARDS die solely as a result of respiratory complications, and the remaining mortality is attributed to other organ failures. In the Parent et al. study, 42% of the canine deaths were attributable to respiratory dysfunction.

**PATHOPHYSIOLOGY**

The best method to understand the pathophysiology of the pulmonary edema associated with ALI/ARDS is Starling’s equation, which defines the normal movement of fluid across the pulmonary membranes. The average osmotic reflection coefficient (σ) is about 0.7 to 0.8 in normal pulmonary tissue and describes the effectiveness of the endothelium in hindering the passage of solutes (i.e., proteins) from the microvasculature into the interstitial compartment. The net effect of Starling’s forces is that fluid and protein move from the vascular space into the interstitial space. The alveolar barrier between the epithelium of the alveolus and the interstitium can be explained with a similar equation in which the flow of fluid across the alveolar barrier is estimated.

**BOX 1**

**Starling’s Equation of Fluid Movement**

\[
Q_r = K_f [(P_{mv} - P_f) - \sigma (\pi_{mv} - \pi_f)]
\]

- \(Q_r\): Amount of fluid filtered per unit of time
- \(K_f\): Permeability of vessels to fluid
- \(P_{mv}\): Hydrostatic pressure of the pulmonary microvasculature
- \(P_f\): Hydrostatic pressure of the interstitial space
- \(\sigma\): Average osmotic reflection coefficient
- \(\pi_{mv}\): Osmotic pressure of the pulmonary microvasculature
- \(\pi_f\): Osmotic pressure of the interstitial space

In dogs, the alveolar barrier is a single cell layer thick, and the epithelial barrier involves the combined passage of solutes (i.e., proteins) from the microvasculature into the interstitial space.
essentially zero in the normal lung. Fluid tends to remain in the interstitial space of the lungs under normal conditions and is removed by the lymphatics.\textsuperscript{19}

In ARDS, $\sigma$ approaches zero because of a loss of endothelial integrity.\textsuperscript{2} This leads to the uncontrolled flow of fluid and protein into the interstitial space, exceeding the capacity of the lymphatic system.\textsuperscript{2,19} Therefore, fluid begins to accumulate in the pulmonary interstitium and the peribronchovascular cuffs. There is also damage to the alveolar epithelium, and fluid and proteins leak from the interstitium into the alveoli, causing alveolar flooding (Figure 1). This is observed on radiographs as a diffuse alveolar pattern.\textsuperscript{19,20}

The reason for the loss of vascular and alveolar integrity has not been fully defined. The pathogenesis of ALI/ARDS is extremely complex and involves numerous inflammatory mediators as well as cellular responses (Figure 1). The time course, order of events, and interactions of these responses are not clearly understood.\textsuperscript{2,6,18–21} Whether there is direct or indirect lung injury, the overall effect is an abnormal modulation and regulation of the inflammatory response that allows the development of ALI/ARDS.\textsuperscript{2,6,18–21} This rogue inflammatory response has both cellular and humoral components.\textsuperscript{2,6,18–21}

The major cellular components are the neutrophil and macrophage; the major humoral components are tumor necrosis factor (TNF)-$\alpha$, interleukin (IL)-1, IL-6, and IL-8.\textsuperscript{2–6,18–21}

**Cellular Components**

**Neutrophil**

Although ALI/ARDS can occur without a primary neutrophilic component, most inciting causes have a strong neutrophil response.\textsuperscript{2–6} The role of the neutrophil follows a sequential pattern. Initially, there is neutrophil sequestration in the lungs, followed by neutrophil adherence, and finally transmigration into the interstitium and alveolar spaces.\textsuperscript{21a} The neutrophil provides a nonspecific defense response that is as equally capable of destroying invading microbes as it is of mediating host tissue damage.\textsuperscript{2–6} Proteases are released along with oxygen radicals that initiate lipid peroxidation, alter surface properties, prevent normal cellular metabolism, damage cellular DNA, and inactivate $\alpha$-antitrypsin.\textsuperscript{2–6} Because $\alpha$-antitrypsin is the major antiprotease located in the lung, its inactivation shifts the antiprotease–protease balance, thereby potentiating the effects of neutrophil proteases.\textsuperscript{2–6}

**Macrophages and Monocytes**

Macrophages comprise more than 90% of the pulmonary leukocyte population in normal lungs and function to regulate the inflammatory and immune response in ALI/ARDS via the release of numerous mediators. TNF-$\alpha$ and IL-1, two of the most critical cy-

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**Figure 1**—The normal alveolus (left) and the injured alveolus in the acute phase of acute lung injury and acute respiratory distress syndrome (right). In the acute phase of this syndrome, there is sloughing of the bronchial and alveolar epithelial cells with the formation of protein-rich hyaline membranes on the denuded basement membrane. Neutrophils are shown adhering to the injured capillary endothelium and marginating through the interstitium into the air space, which is filled with protein-rich edema fluid. (From Ware LB, Matthay MA: Medical progress: The acute respiratory distress syndrome. *N Engl J Med* 342(18):1339, 2000; with permission.)
tokines, are released from the macrophage along with 
IL-6 and IL-8. The macrophage can also move into 
the interstitial and alveolar spaces and release oxygen-
derived free radicals, proteases, and metalloproteinases, 
further increasing the protease burden of the lungs.

**Lymphocytes**
Recent evidence suggests that lymphocytes play a role 
in the evolution of ALI/ARDS. Lymphocytes undergo 
activation, sequestration, adhesion, and chemotaxis in 
much the same manner as the neutrophil and use many 
of the same chemotactants. Although their function in 
ALI/ARDS is not fully understood, these cells can pro-
duce damage similar to that observed in ALI/ARDS; 
therefore, their role in the disorder needs further inves-
tigation.

**Platelets and Fibroblasts**
Platelet aggregation leads to microvascular emboliza-
tion and the production of various cytokines and 
eicosanoids. These mediators result in vasoconstriction 
and bronchoconstriction and can lead to further vascu-
lar and alveolar membrane damage. Fibroblasts and 
type II pneumocytes synthesize and release many com-
plement components (e.g., C3, C5).

**Humoral Components**

**Complement**
Complement can be activated by one of three path-
ways (i.e., classical antibody dependent, alternative, or 
the newly discovered mannan-binding lectin/mannan-
binding lectin–associated serine proteases). Following 
activation, the proinflammatory peptides C3a and C5a 
(commonly called anaphylatoxins) and the membrane 
attack complex (C5b–9) are formed. These lead to 
chemotaxis of leukocytes, degranulation of all granulo-
cytes, smooth muscle contraction, increased vascular 
permeability, and stimulation of the production and re-
lease of arachidonic acid metabolites and cytokines.

**Cytokines**
Several different biochemical mediators have been 
grouped into the general category of cytokines. Fortu-
nately, the primary cytokines involved with ALI/ARDS 
can be loosely placed into four general functional categ-
ories (Table 1). These cell-derived peptides cause alter-
ation of one or more functions in target cells, which 
elicit a direct effect or stimulate the production of more 
humoral mediators (Box 2). Undoubtedly, this is a 
complex system and all the cytokines involved have 
likely not been identified. TNF-α, IL-1, IL-6, and IL-8 
are the cytokines suspected of having the greatest im-
 pact on the development and eventual outcome of 
ALI/ARDS.

**Eicosanoids**
Eicosanoids are the product of arachidonate metabo-
lism and as such are products of membrane phospholipid 
metabolism. There are three major categories depend-
ing on the specific metabolic pathway used. Prostaglandins, including thromboxanes TXA and TXB, 
and prostacyclins are produced via the cyclooxygenase 
pathway. Leukotrienes and epoxides are derived from 
the lipoxgenase and monoxygenase pathways, respec-
tively. The prostaglandins and leukotrienes are suspect-
ed to be the major players in the pathogenesis of 
ALI/ARDS. Recent evidence indicates that their princi-
pal role lies in the modulation of the inflammatory 
process via stimulation of cytokine synthesis and re-

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**TABLE 1**

<table>
<thead>
<tr>
<th>Cytokine Type</th>
<th>Functional Category</th>
</tr>
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<tbody>
<tr>
<td>Initiation</td>
<td>TNF-α, IL-1</td>
</tr>
<tr>
<td>Recruitment</td>
<td>IL-8; macrophage inflammatory peptide (MIP)-1, MIP-2; monocyte chemotactic factor (MCF)–1, MCF-1α; transforming growth factor (TGF)–β</td>
</tr>
<tr>
<td>Repair</td>
<td>TGF-α, TGF-β; platelet-derived growth factor, insulinlike growth factor</td>
</tr>
<tr>
<td>Resolution</td>
<td>TGF-β, IL-4, IL-6, IL-10, IL-1 receptor agonist</td>
</tr>
</tbody>
</table>

**BOX 2**

**Typical Actions Elicited by Cytokines Involved in the Pathogenesis of ALI/ARDS**

- Apoptosis (programmed cell death)
- Stimulation of other cells to release cytokines
- Monocyte, neutrophil, and platelet chemotaxis and activation
- Cytotoxicity (endothelial and epithelial)
- Mediated bioactivity (vasoactivity and bronchoactivity)
- Inhibited surfactant function
- Elevated production of histocompatibility antigen
- Precipitation of angiogenesis
- Stimulation of arachidonate metabolism (production of eicosanoids)
- Stimulation of monocyte formation in bone marrow
- Stimulation of leukocyte adhesion to the vascular endothelium
lease.2–6 Eicosanoids also elicit potent tissue level responses (e.g., vasoconstriction, bronchoconstriction) that indirectly damage endothelial and epithelial tissue and further potentiate the pathophysiologic effects of ALI/ARDS.2–6

Other Mediators

Endogenous nitric oxide, growth factors, and pulmonary neuropeptides (e.g., substance P) are also involved in the pathogenesis of ALI/ARDS.2–6 Although their exact role is not clearly understood, it is known that at certain stages of the disease process there is either an excess or depletion of these mediators.2–6

Surfactant

Until recently, the role of surfactant in the pathophysiology of ALI/ARDS was not fully appreciated.2–6 Often there is direct damage to type II pneumocytes, leading to a decrease in the surfactant pool.2–6 Oxygen radicals and proteases have been shown to damage the surfactant molecule, and arachidonic acid metabolites and cytokines are also known to inhibit the production and function of surfactant. Plasma leaking into the alveolar spaces can also lead to inactivation of surfactant as well as a washing away or dilutional effect that will lead to a loss of activity.2–6 Research is currently underway to assess the potential role of surfactant therapy in ALI/ARDS.2

PATHOGENESIS

Acute lung injury/ARDS results from direct or indirect injury to the vascular endothelium or alveolar epithelium. This leads to activation of the humoral and cellular components, which initially begin as a localized inflammatory response. For some unknown reason, this response expands to involve the entire pulmonary system. Suspected causes include inappropriately high or low cytokine production, inappropriate response to systemic cytokines, alteration in cytokine metabolism, and reperfusion injury. None of these theories, however, has been proven.23

Activation of inflammatory mediators leads to increased permeability of the pulmonary vasculature and/or alveolar tissue, allowing the free movement of fluid and protein into the interstitium and/or alveolar spaces.2–6 As the edema increases, more fluid floods the alveoli. Because the alveoli are likely to still be perfused, an increased shunt fraction is produced.2–6 Without ventilation, this perfusion produces the hallmark sign of ALI/ARDS, namely hypoxemia refractory to increasing amounts of oxygen.2–6 Additionally, the increase in fluid in the interstitial space acts to decrease the functional residual capacity of the lungs and leads to airway closure as well as distal lung atelectasis.20 Congestion in the lungs also leads to decreased compliance.20 This alteration in compliance decreases the elastic recoil of the lungs as well as the resting volume of the lungs, thus increasing the work of breathing.24 This can further complicate the hypoxemia and lead to increased lactic acidosis.2–6

Such a large-scale inflammatory response then allows mediators to spill over into the systemic circulation, leading to activation of systemic inflammation.2–6 Additionally, hypoxemia can cause hypoxic organ damage, alterations in systemic blood flow, and increased potential for reperfusion injury.2–6 Thus ALI/ARDS can easily lead to the production of SIRS and also multisystem organ dysfunction and MOFS.2–6

CLINICAL FINDINGS

Although signs may be delayed for 1 to 3 days, patients are usually seen within 24 hours of the inciting event.7 Owner complaints usually include dyspnea, lethargy, anorexia, trauma, or collapse.14 ALI/ARDS may also develop acutely in critically ill hospitalized patients with underlying risk factors. Physical examination routinely discloses tachypnea, dyspnea, increased abdominal effort, crackles, and harsh lung sounds.14 Hypotension and fever as well as hypoxemia that is refractory to oxygen treatment may also be seen.7 In the early stages, only dyspnea may be observed.19 The most common radiographic finding is the presence of diffuse alveolar infiltrates in all lung lobes5,14 (Figure 2). The cardiac silhouette and pulmonary vasculature appear normal, thereby ruling out heart failure.5,18 Bronchoalveolar lavage fluid can show an increased protein or neutrophil content.2–6,8,13,15–26

Clinical diagnosis in humans is based on establishing an association with a known risk factor, the timing of the onset (acute), no evidence of left atrial hypertension (normally signified by a pulmonary wedge pressure less than 18 mm Hg), evidence of diffuse bilateral pulmonary edema, and a PaO2:FiO2 less than 300 mm Hg for ALI and less than 200 mm Hg for ARDS.2–6 This ratio indicates how responsive the hypoxemia is to oxygen therapy and how much of the hypoxemia results from the shunt fraction. PaO2:FiO2 is a good clinical indicator of the severity of ALL. In veterinary medicine, it is uncommon to place a catheter for measuring pulmonary wedge pressure; therefore, it is difficult to meet the established criteria for diagnosis used in human medicine. In veterinary patients, the diagnosis is highly suggested by finding hypoxemia and alveolar infiltrates in the absence of congestive heart failure. It is better to proceed suspecting a diagnosis of ALI/ARDS and to continue to monitor for this syndrome rather than have it occur unexpectedly.

Common diagnostic differentials include other caus-
es of pulmonary edema (cardiogenic or neurogenic), acute pneumonia, allergic pneumonitis, interstitial fibrosis, pulmonary lymphoma, pulmonary contusions, and aspiration pneumonia. Another consideration might be pulmonary thromboembolic disease.

**TREATMENT**

To date, there is no specific treatment for ALI/ARDS. Management remains supportive and is aimed at treating the underlying cause and maintaining adequate oxygen delivery to the tissues. The primary goals of therapy should be to (1) find and treat the cause, (2) minimize edema accumulation, (3) provide supportive treatment as indicated, and (4) avoid hypotension, volume overload, oxygen toxicity, and infection.

Because this disease might potentially lead to other more life-threatening disorders, the key to successful management lies in anticipation. Therefore, critical parameters should be assessed at least twice daily to ensure that the animal’s condition does not deteriorate. Purvis and Kirby have developed 20 critical parameters that should be monitored when treating animals with SIRS. Monitoring of these same parameters should prove beneficial in the treatment of ALI/ARDS or any critically ill patient, provided that the proper response for each parameter is followed.

**Treating the Underlying Cause**

The first principle in the management of ARDS is to locate and treat the underlying cause. If possible, the initial insult must be arrested to prevent further activation of the inflammatory response. An exhaustive search for the cause should be conducted, including radiography of the thorax and abdomen as well as abdominal ultrasonography. Intraabdominal sepsis is a common cause in humans and may be a predisposing factor in dogs as well. Surgery should be preformed (if necessary) to drain an abscess, remove necrotic bowel, resolve a stump pyometra, or treat peritonitis. Clinicians should not be reluctant to perform an exploratory laparotomy on any patient that is acutely ill with lung injury and severely compromised pulmonary function because correction of the underlying cause may be the patient’s only hope for survival. Broad-spectrum antibiotics should be started pending results of appropriate cultures. If sepsis is suspected or no inciting cause can be found, broad-spectrum antibiotics should be started based on the presumption that there is an unlocated infectious cause.

**Monitoring and Supportive Treatment**

**Oxygenation and Ventilation**

Some patients with ALI/ARDS may maintain adequate oxygenation with spontaneous ventilation; however, supplemental oxygen therapy is needed when the arterial oxygen saturation drops below 90%, PaO₂ drops below 60 mm Hg, or when it is beneficial to decrease the work of breathing. Oxygen therapy is instituted to achieve three clinical goals: (1) treat the hypoxemia, (2) decrease the work of breathing, and (3) decrease the myocardial workload. If the dog is oxygen-responsive (as observed in the early stages of ALI/ARDS), then one of the four common oxygen delivery methods should be used (Table 2). The first method is via an oxygen mask. However, many animals will not tolerate mask insufflation and, therefore, their oxygen demand will be increased by their struggling, thereby defeating the purpose of the mask (Figure 3A). The second
method is nasal insufflation,\textsuperscript{24,29} which allows patients some freedom of movement, but Fi\textsubscript{O\textsubscript{2}} cannot be determined accurately (Figures 3B and 3C).\textsuperscript{24,29} An oxygen flow rate of 50 to 100 ml/kg will generally deliver an Fi\textsubscript{O\textsubscript{2}} of 0.4.\textsuperscript{29} Higher Fi\textsubscript{O\textsubscript{2}} (greater than 0.5) for more than 24 hours can lead to oxygen toxicity.\textsuperscript{29} In this situation, oxygen free radicals can produce direct damage to the lungs, thus providing a second risk factor for the development of ALI/ARDS. A third method of oxygen supplementation is to use an oxygen cage to provide a defined Fi\textsubscript{O\textsubscript{2}} in a controlled environment.\textsuperscript{24,29} The disadvantage of this method is that opening the cage for treatment will cause a loss of the high Fi\textsubscript{O\textsubscript{2}} environment.\textsuperscript{24,29} It is also difficult to maintain proper humidity and temperature without a specialized oxygen cage. A final method is to use intratracheal oxygen by placing an endotracheal tube or transtracheal catheter.\textsuperscript{24,29} As mentioned previously, prolonged exposure to high levels of oxygen can result in direct injury to the lungs.\textsuperscript{24,29} Inspired oxygen levels less than 50% are considered to be safe for long-term ventilation, but clinicians should not hesitate to use Fi\textsubscript{O\textsubscript{2}} greater than 0.5 initially.\textsuperscript{30} To minimize the risk of oxygen radical damage to the lungs, it is important to use the lowest level of oxygen supplementation that will provide a Pa\textsubscript{O\textsubscript{2}} between 70 and 90 mm Hg and/or an oxygen saturation by pulse oximeter (Sp\textsubscript{O\textsubscript{2}}) greater than 90%.\textsuperscript{24,29}

In many patients suffering from hypoxemia caused by shunting and ventilation/perfusion mismatch, positive end-expiratory pressure (PEEP) can provide an alternative to increasing the Fi\textsubscript{O\textsubscript{2}} to dangerously high levels.\textsuperscript{31} PEEP is a method of increasing the end-expiratory lung volume by allowing positive pressure to remain in the airways at the end of expiration.\textsuperscript{31} PEEP is not a mode of ventilation but an addition to other modes of ventilation. For example, intermittent mandatory ventilation is a mode of mechanical ventilation that can be modified with the addition of PEEP. It can be applied to both spontaneous and mechanically ventilated patients but usually is employed in conjunction with mechanical ventilation.\textsuperscript{31} PEEP is primarily indicated for those conditions in which there is arterial hypoxemia present despite adequate ventilation.\textsuperscript{31} The best PEEP levels have not been determined. Recommendations are to start with a PEEP of 5 cm water and increase in 3- to 5-cm increments up to a maximum pressure of 15 to 20 cm water to achieve an Sp\textsubscript{O\textsubscript{2}} greater than 90% with a minimal Fi\textsubscript{O\textsubscript{2}} while maintaining a reasonable cardiovascular status.\textsuperscript{3} It is important to remember that the higher the PEEP, the greater the decrease in cardiac output and risk of barotrauma to the lungs.

If the patient is suffering from respiratory muscle fatigue, respiratory acidosis, or hypercapnia; has difficulty with oxygenation (despite high levels of supplemental oxygen); or needs its airway protected from aspiration, then intubation and mechanical ventilation are indicated\textsuperscript{1} (Figures 3D and 3E). Assisted control ventilation, which allows the patient to initiate each breath with little effort and provides a backup respiratory rate in case the patient fails to initiate enough breaths, is the mode that is most often attempted initially.\textsuperscript{5} Typically, Fi\textsubscript{O\textsubscript{2}} is started at 1.0 and reduced in small increments to a level that maintains the Sp\textsubscript{O\textsubscript{2}} greater than 90%.\textsuperscript{5} Intermittent mandatory ventila-

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**TABLE 2**

<table>
<thead>
<tr>
<th>Method</th>
<th>Advantage</th>
<th>Disadvantage</th>
<th>Flow Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen mask</td>
<td>Easy to use</td>
<td>Animals often struggle, thereby increasing oxygen demand</td>
<td>Not established</td>
</tr>
<tr>
<td>Nasal insufflation</td>
<td>Freedom of movement</td>
<td>Fi\textsubscript{O\textsubscript{2}} cannot be accurately determined (estimated at 40%)</td>
<td>50–100 ml/kg/min</td>
</tr>
<tr>
<td>Oxygen cage</td>
<td>Provides defined Fi\textsubscript{O\textsubscript{2}} level in a controlled environment</td>
<td>Opening the cage will cause a loss of the established Fi\textsubscript{O\textsubscript{2}}</td>
<td>As needed to maintain desired Fi\textsubscript{O\textsubscript{2}}</td>
</tr>
<tr>
<td>Intratracheal oxygen</td>
<td>Allows control of respiration and Fi\textsubscript{O\textsubscript{2}} with a ventilator</td>
<td>Requires the animal to be under chemical restraint</td>
<td>20–40 ml/kg/min or as needed to maintain Fi\textsubscript{O\textsubscript{2}} if on a ventilator</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Use the lowest Fi\textsubscript{O\textsubscript{2}} that will provide a Pa\textsubscript{O\textsubscript{2}} between 70 and 90 mm Hg or an Sp\textsubscript{O\textsubscript{2}} greater than 90%.

\textsuperscript{b}Serial monitoring of the Pa\textsubscript{O\textsubscript{2}} and/or Sp\textsubscript{O\textsubscript{2}} is necessary to ensure proper management.

Fi\textsubscript{O\textsubscript{2}} = fractional inspired oxygen; Pa\textsubscript{O\textsubscript{2}} = partial pressure of arterial oxygen; Sp\textsubscript{O\textsubscript{2}} = oxygen saturation by pulse oximeter.
tion allows the patient to breathe spontaneously, but a positive-pressure breath is delivered by the ventilator at predetermined intervals. Continuous positive pressure ventilation is achieved by having the ventilator control all aspects of ventilation.

Serial monitoring of arterial blood gas and continuous monitoring of SpO₂ values are essential to ensure proper management and treatment. Additionally, these will serve as guides to ensure that the lowest PEEP and FiO₂ are used to prevent further injury to the lungs via barotrauma or oxygen radical formation.

Fluid Balance

In human medicine, two hotly debated views have emerged in regard to fluid balance. The first approach is to decrease pulmonary capillary wedge pressure as low as possible. This will require the use of vasopressor therapy as well as inotropic agents to maintain adequate systemic perfusion. The theory is that reduction of the pulmonary capillary wedge pressure will minimize the amount of fluid that will leak across the membranes. This method requires careful and constant monitoring to ensure that renal function is maintained. The second strategy stems from the evi-
pressure while avoiding fluid overload.

**Blood Pressure**

The systolic blood pressure must remain above 90 mm Hg; more importantly, the mean arterial blood pressure must be maintained above 60 mm Hg to ensure adequate renal perfusion. If hypotension occurs, then therapeutic intervention must be considered.

**Coagulation**

Disseminated intravascular coagulation is a potential sequela of ALI/ARDS; therefore, it is important to check for coagulation abnormalities. Daily platelet counts and activated clotting times are the minimum laboratory tests that should be performed. Prothrombin and partial thromboplastin time, fibrin degradation products, antithrombin III, and fibrinogen can also be monitored. Early in DIC, platelet numbers will decline and coagulation times will be shortened. As DIC progresses, coagulation times and fibrin degradation products increase, whereas antithrombin III levels decrease.

**Erythrocytes/Hemoglobin**

Because ALI/ARDS alters the oxygenation ability of animals, it is important to maintain the hematocrit greater than 20% and ideally greater than 30%. Likewise, hemoglobin should be maintained above 7 to 10 g/dl.

**Renal Function**

Urine output, blood urea nitrogen, and serum creatinine should be monitored daily, and routine urinalyses should be performed. It is not uncommon for patients to die as a result of acute renal failure secondary to ischemic injury during ALI/ARDS; therefore, adequate blood pressure must be maintained. Urine output should be at least 1 to 2 ml/kg/hr in patients with adequate renal blood flow.

**Nutrition**

Nutrition is important from the time the animal enters the hospital. Due to the labor of breathing and the high metabolic rate from the inflammatory response,
ALI/ARDS patients are in a negative energy balance.\textsuperscript{2–5,31} Clinically, this malnutrition can lead to compromise of host defenses, loss of muscle strength, visceral organ atrophy, pneumonia, sepsis, and even death.\textsuperscript{31} Additional studies have shown that disuse of the bowels may also predispose animals to secondary bacterial translocation and sepsis.\textsuperscript{31} The goal is to provide 25% of the patient’s caloric requirement within the first 24 hours and to increase this amount to 75% to 80% within 72 to 96 hours.\textsuperscript{31} If the patient is willing to eat, then oral supplementation can begin; however, a feeding tube should be used if the animal is unwilling or unable to eat.\textsuperscript{31}

**Nursing Care and Patient Mobilization**

Recumbent patients should be turned and their limbs manipulated every 4 hours.\textsuperscript{31} Fecal material and urine should be removed immediately and all catheter and tube sites should be checked as well as properly labeled to avoid confusion or misuse.\textsuperscript{31}

**Pharmacologic Treatment**

Several studies\textsuperscript{2–6} indicate that there is little if any benefit in using corticosteroids early in the course of ALI/ARDS, and their use may actually increase the duration of the disease. Furthermore, the use of corticosteroids in septic patients did not prevent them from developing ALI/ARDS.\textsuperscript{2–6} Another study\textsuperscript{31} indicated that the use of corticosteroids in the fibroproliferative stage of ARDS reduced mortality and increased the PaO\textsubscript{2}/FiO\textsubscript{2} ratio. Current recommendations in humans are that corticosteroids be used in the latter stages of ARDS.

Inhaled nitric oxide causes vasodilation of pulmonary vasculature, resulting in improvement of the shunt fraction and thus decreasing hypoxia.\textsuperscript{2–6} However, nitric oxide can produce severe side effects (e.g., combining with oxygen to produce nitric acid). It also produces methemoglobinemia and may worsen leakage by increasing vascular permeability. Therefore, it is not recommended for treatment of ALI/ARDS.\textsuperscript{2–6}

The antioxidants vitamins C and E are oxygen radical scavengers and as such will reduce lung injury.\textsuperscript{2–6} Overdosing, however, can lead to prooxidant effects that will result in increased lung damage.\textsuperscript{2–6} Ketoconazole has had limited success in preventing the development of ALI/ARDS in some small, randomized trials by functioning as a TXA\textsubscript{2} blocker.\textsuperscript{4} Superoxide dismutase and catalase are oxygen radical scavengers that have been shown to reduce the lung injury associated with pancreatitis in dogs.\textsuperscript{35}

**Outcome**

Most human survivors of ALI/ARDS have little impairment following recovery.\textsuperscript{2–5} In most patients, lung mechanics return to normal within 1 year following resolution of the acute illness.\textsuperscript{2–4} (Figure 4). In a few survivors, however, there are severe alterations in the normal pulmonary architecture that can lead to thickening of all pulmonary surfaces. These changes result in a decreased diffusing capacity and increased dead space. This situation is dangerous and can lead to pronounced hypoxia and dyspnea during exercise.\textsuperscript{2–5} To date, there are no reports in the literature of any dog that has survived ALI/ARDS; therefore, little is known about the outcome of this disease in dogs.

**Conclusion**

Acute lung injury/ARDS is seldomly reported in veterinary medicine. It is expected that the number of cases will continue to rise because of increased awareness and advances in emergency and critical care medicine. Despite 30 years of research of this syndrome in humans, little is known about the exact pathogenesis of this disease. This lack of knowledge has prevented the development of specific treatment protocols. Supportive care remains the primary treatment modality, and recent advances have provided prolonged survival as evidenced by the fact that only 20% of patients succumb to ARDS alone. Unfortunately, patients often progress from ARDS into SIRS and/or multisystem organ dysfunction and/or MOFS, thus resulting in an overall mortality rate of 50% to 70% in humans. Vigilant monitoring of patients and anticipating rather than reacting to the changing conditions may serve to lower this rate. It is hoped that specific treatments will become available in the future to allow for easier treatment and improved survival.

**References**

8. Türk J, Miller M, Broen T, et al: Coliform septicemia and pulmonary disease associated with canine paroviral enter-
1. Which of the following is not a common risk factor for the development of ALI/ARDS?
   a. microbial pneumonia
   b. sepsis
   c. aspiration pneumonia
   d. tracheitis

2. Which of the following cytokines does not have a major impact on the development of and eventual outcome of ALI/ARDS?
   a. TNF-α
   b. IL-2
   c. IL-1
   d. IL-6

3. Inactivation of α-antitrypsin leads to which detrimental event?
   a. shifting the antiprotease–protease balance, thereby potentiating the effects of proteases
   b. oxygen radicals initiating lipid peroxidation
   c. alteration of normal cellular metabolism
   d. damage to cellular DNA

4. Which eicosanoids are suspected to be the major players in the pathogenesis of ALI/ARDS?
   a. prostaglandins
   b. TXA₂
   c. leukotrienes
   d. prostacyclins

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6. Which of the following is not a common risk factor for the development of ALI/ARDS?
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7. Which of the following cytokines does not have a major impact on the development of and eventual outcome of ALI/ARDS?
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8. Inactivation of α-antitrypsin leads to which detrimental event?
   a. shifting the antiprotease–protease balance, thereby potentiating the effects of proteases
   b. oxygen radicals initiating lipid peroxidation
   c. alteration of normal cellular metabolism
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9. Which eicosanoids are suspected to be the major players in the pathogenesis of ALI/ARDS?
   a. prostaglandins
   b. TXA₂
   c. leukotrienes
   d. prostacyclins

The article you have read qualifies for 1.5 contact hours of Continuing Education Credit from the Auburn University College of Veterinary Medicine. Choose the best answer to each of the following questions; then mark your answers on the postage-paid envelope inserted in Compendium.
5. What is the hallmark clinical sign of ARDS?
   a. oxygen-responsive hypoxia
   b. patchy bilateral pulmonary infiltrates
   c. non-oxygen-responsive hypoxia
   d. pulmonary wedge pressure less than 18 mm Hg

6. Which of the following is not required for the clinical diagnosis of ARDS?
   a. evidence of diffuse bilateral pulmonary edema
   b. alveolar oxygen:inspired oxygen concentration less than 200 mm Hg
   c. pulmonary wedge pressure less than 18 mm Hg
   d. PEEP greater than 5 cm water

7. $\text{PaO}_2:\text{FiO}_2$ ratio is a good clinical indicator of the
   a. severity of ALI.
   b. amount of surfactant.
   c. flow rate of oxygen needed.
   d. cause of the ALI.

8. An inspired oxygen concentration less than _____% is considered safe.
   a. 55
   b. 60
   c. 50
   d. 1

9. Optimum PEEP levels
   a. have not been determined.
   b. should not exceed 15 to 20 cm water.
   c. maintain $\text{SpO}_2$ greater than 90%.
   d. all of the above

10. Corticosteroids are recommended in the treatment of which phase of ARDS?
    a. acute phase
    b. fibroproliferative phase
    c. intermediate phase
    d. Steroids should never be used in the treatment of ARDS.